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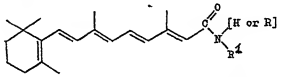
(54) ACID AMIDES

(71) We, F. HOFFMANN-LA ROCHE & Co., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to acid amides. More particularly, it is concerned with a vitamin A acid amides and a process for the manufacture thereof.

The vitamin A acid amides provided by this invention have the following general formula

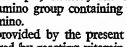


(I)

wherein R and R^1 each represent an alkyl group containing from 1 to 10 carbon atoms [which may be substituted by a lower alkoxy group or a di(lower alkyl) amino group], a hydroxy-(lower alkyl) group, the phenyl group or the benzyl group.

The alkyl group referred to earlier can be a straight-chain or branched-chain hydrocarbon group containing from 1 to 10 carbon atoms for example methyl, ethyl, propyl, *iso*propyl, *n*-butyl, *tert*butyl, pentyl, hexyl, heptyl, *n*-decyl and the like. The term "hydroxy-(lower alkyl) group" signifies a hydroxy-alkyl group containing from 1 to 4 carbon atoms such as, for example, the hydroxyethyl group. The term "lower alkoxy group" signifies a straight-chain or branched-chain alkoxy group containing from 1 to 4 carbon atoms, for example, methoxy and ethoxy. The term "lower alkylamino group" signifies an alkylamino group containing from 1 to 4 carbon atoms, for example, methylamino or ethylamino.

According to the process provided by the present invention, the vitamin A acid amides aforesaid are manufactured by reacting vitamin A acid or a functional derivative thereof with an amine of the general formula



(II)

wherein R and R^1 have the significance given earlier.

As functional derivatives of vitamin A acid there can especially be named the vitamin A acid halides, preferably the chloride, as well as the vitamin A acid esters. A preferred amine of formula II is ethyl amine.

The reaction is expediently carried out in an inert organic solvent, for example, ether and at a temperature of from about room temperature up to the reflux temperature of the reaction mixture.

The reaction is also expediently carried out under an inert gas atmosphere, for example, under a nitrogen atmosphere.

The vitamin A acid amides provided by the present invention can be used for

the topical and systemic therapy of precanceroses and carcinomas and for the systemic and topical prophylaxis of carcionomas. For these purposes, they can be used as such or in combination with cytostatic products as well as with irradiations. Furthermore, they can be used for the topical and systemic therapy of acne, psoriasis and other dermatological disorders proceeding with increased or pathologically altered cornification. They can also be used in disorders of the mucous membranes which proceed with inflammatory or degenerative or metaplastic alterations. A preferred vitamin A acid amide of formula I is vitamin A acid ethyl amide.

The toxicity tests carried out in the mouse and rat gave the following results for the acute toxicity:

A) *Rat:*

Vitamin A acid ethyl amide in rape oil

	mg/kg *p.o.* or mg/kg *i.p.*	
	24 hours	10 days
DL_{10}	>4000	>4000
DL_{50}	>4000	>4000
DL_{90}	>4000	>4000

B) *Mouse:*

1) Vitamin A acid ethyl amide in rape oil

	mg/kg *p.o.* or mg/kg *i.p.*		
	24 hours	10 days	20 days
DL_{10}	>4000	>4000	>4000
DL_{50}	>4000	>4000	>4000
DL_{90}	>4000	>4000	>4000

2) Vitamin A acid ethanol amide in rape oil

	mg/kg *i.p.*	
	24 hours	10 days
DL_{10}	>4000	710
DL_{50}	>4000	1000
DL_{90}	>4000	1400

3) Vitamin A acid diethyl amide, vitamin A acid *n*-butyl amide, vitamin A acid phenyl amide, vitamin A acid *iso*propyl amide, vitamin A acid methyl amide in rape oil.

	mg/kg *i.p.*	
	24 hours	10 days
DL_{10}	>4000	>4000
DL_{50}	>4000	>4000
DL_{90}	>4000	>4000

The vitamin A acid amides provided by the present invention have a marked epithelium-protecting action (determined in accordance with BOGUTH *et al.* Int. Z. Vitaminf. 1960, *31*, 6), but in contrast to the free vitamin A acid and vitamin A acid amide itself they cause no skin irritation and no so-called A-hypervitaminosis.

The vitamin A acid amides of formula I hereinbefore can be used as medicaments; for example, in the form of pharmaceutical preparations which contain them in association with a compatible pharmaceutical carrier.

The pharmaceutical preparations serving for systemic application can be manufactured by adding a vitamin A acid amide of formula I as the active ingredient to non-toxic, inert, solid or liquid carriers which are usual *per se* in such preparations.

The pharmaceutical preparations can be administered enterally or parenterally. Suitable for enteral application are, for example, preparations in the form of tablets, capsules, dragées, syrups, suspensions, solutions as well as suppositories. Preparations in the form of infusion or injection solutions are suitable for parenteral application.

The dosages in which the present vitamin A acid amide are administered can vary according to the kind and route of application and according to the requirements of the patient. They can be administered in amounts of up to 1000 mg daily in one or more doses.

A preferred form of presentation is capsules with a content of about 50 mg to about 200 mg of a vitamin A acid amide of formula I. Capsules of hard or soft gelatin, methyl cellulose or of another suitable material which is well dissolved in the digestive tract are suitable.

The pharmaceutical preparations can contain inert additives or also other medicinally active additives. Tablets or granules, for example, can contain a series of binding agents, fillers, carriers or diluents. Liquid preparations can, for example, exist in the form of a sterile water-miscible solution. Besides the vitamin A acid amide, capsules can also contain a filling material or thickening agent. Furthermore, there can also be present flavour-improving additives, as well as the substances usually used as preservatives, stabilising agent, moisture-retaining agents or emulsifiers. Salts for varying the osmotic pressure, buffers or other additives can also be present.

The carriers and diluents mentioned hereinbefore can consist of organic or inorganic substances; for example, of water, gelatin, lactose, starches, magnesium stearate, talc, gum arabic, polyalkylene glycols. A prerequisite is that all adjuvants used in the manufacture of the preparations are non-toxic.

For topical application, the vitamin A acid amides of formula I can expediently be used in the form of ointments, tinctures, creams, solutions, lotions, sprays or suspensions. Ointments and creams, as well as solutions, are preferred. These preparations serving for topical application can be manufactured by mixing a vitamin A acid amide of formula I, as the active ingredient, with non-toxic, inert, solid or liquid carriers suitable for topical treatment which are usual *per se* in such preparations.

For topical application, there are expediently used about 1% to about 10%, preferably about 2% to about 5% solutions and about 1% to about 10%, preferably about 2% to about 5%, ointments or creams.

The vitamin A acid amides can also be used together with an antioxidant. Of

these, there especially come into consideration tocopherols, N-methyl-γ-tocopheramine as well as butylated hydroxyanisole, butylated hydroxytoluene or ethoxyquin.

The following Examples illustrate the process provided by the invention:

EXAMPLE 1

60 parts by weight of ethylamine and 300 parts by volume of absolute ether are stirred with ice-cooling under a nitrogen atmosphere and the acid chloride from 30 parts by weight of vitamin A acid in 100 parts by volume of absolute ether is added dropwise within 30 minutes. The mixture is stirred at room temperature for 4 hours and further for 2 hours at reflux. Then the mixture is cooled, diluted with 1000 parts by volume of ether and washed four times with 100 parts by volume of water each time. The ether solution is dried over sodium sulphate, the solvent is evaporated off and the residue is crystallized from a benzene/hexane mixture. There is obtained vitamin A acid ethyl amide with a melting point of 137°—138°C; λ_{max}=347 mμ, $E^{1\%}_{1\ cm}$ 1540.

EXAMPLE 2

The following vitamin A acid amides can be manufactured in a manner analogous to that described in Example 1:

Vitamin A acid methyl amide

m.p. 174°—175°C; λ_{max} 345 mμ, $E^{1\%}_{1\ cm}$ 1645

Vitamin A acid *iso*propyl amide

m.p. 134°—135°C; λ_{max} 345 mμ, $E^{1\%}_{1\ cm}$ 1515

Vitamin A acid butyl amide

m.p. 92°—93°C; λ_{max} 347 mμ, $E^{1\%}_{1\ cm}$ 1430

Vitamin A acid methyl propyl amide

m.p. 112°—113°C; λ_{max} 347 mμ, $E^{1\%}_{1\ cm}$ 1462

Vitamin A acid *n*-decyl amide

m.p. 71°—72°C; λ_{max} 347 mμ, $E^{1\%}_{1\ cm}$ 1163

Vitamin A acid ethanol amide

m.p. 138—139°C; λ_{max} 347 mμ, $E^{1\%}_{1\ cm}$ 1475

Vitamin A acid phenyl amide

m.p. 146°—147°C; λ_{max} 362 mμ, $E^{1\%}_{1\ cm}$ 1450

Vitamin A acid diphenyl amide

m.p. 116°—117°C; λ_{max} 368 mμ, $E^{1\%}_{1\ cm}$ 1130

Vitamin A acid benzyl amide

m.p. 104°—105°C; λ_{max} 350 mμ, $E^{1\%}_{1\ cm}$ 1220

Vitamin A acid 2-diethylamino-ethyl amide

m.p. 86°—87°C; λ_{max} 347 mμ, $E^{1\%}_{1\ cm}$ 1310

Vitamin A acid 2-methoxy-ethyl amide

m.p. 86°C; λ_{max} 348 mμ, $E^{1\%}_{1\ cm}$ 1352

EXAMPLE 3

Vitamin A acid diethyl amide is manufactured in a manner analogous to that described in Example 1. For purification, the amide is chromatographed on 600 g of aluminium oxide (activity III neutral) by means of hexane, the pure amide passing through with hexane after a prefraction has been separated off. After removal of the solvent, vitamin A acid diethyl amide is obtained as an oil; λ_{max} 340 mμ, $E^{1\%}_{1\ cm}$ 1300.

EXAMPLE 4

The following vitamin A acid amides can be manufactured in an analogous manner to that described in Examples 1 and 3.

Vitamin A acid di(*n*-butyl) amide

λ_{max} 337 mμ, $E^{1\%}_{1\,cm}$ 985

Vitamin A acid di(*n*-decyl) amide

λ_{max} 337 mμ, $E^{1\%}_{1\,cm}$ 775

The following Examples illustrate pharmaceutical preparations containing the vitamin A acid amides provided by the invention:

EXAMPLE A

A 2% ointment of the following composition is manufactured in the usual manner:

Vitamin A acid ethyl amide	2.0 g
Cetyl alcohol	2.4 g
Lanolin	6.0 g
White petroleum jelly	51.6 g
Distilled water	*ad* 100.0 g

EXAMPLE B

A 2% solution of the following composition is manufactured in the usual manner:

Vitamin A acid ethyl amide	2 g
Rectified spirit (94%)	70 g
Propylene glycol	*ad* 100 ml

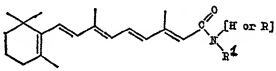
EXAMPLE C

Soft gelatin capsules of the following composition are manufactured in the usual manner:

Vitamin A acid ethyl amide	20.0 mg
Wax mixture	51.5 mg
Vegetable oil	103.0 mg
Sequestrene	0.5 mg

WHAT WE CLAIM IS:—

1) Vitamin A acid amides of the general formula



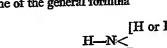
(I)

wherein R and R^1 each represent an alkyl group containing from 1 to 10 carbon atoms [which may be substituted by a lower alkoxy group or a di(lower alkyl) amino group], a hydroxy-(lower alkyl) group, the phenyl or the benzyl group.

2) Vitamin A acid methyl amide.
3) Vitamin A acid ethyl amide.
4) Vitamin A acid *iso*propyl amide.
5) Vitamin A acid butyl amide.
6) Vitamin A acid *n*-decyl amide.
7) Vitamin A acid ethanol amide.
8) Vitamin A acid 2-methoxy-ethyl amide.
9) Vitamin A acid 2-diethylamino-ethyl amide.
10) Vitamin A acid phenyl amide.
11) Vitamin A acid benzyl amide.
12) Vitamin A acid diethyl amide.
13) Vitamin A acid di(*n*-butyl) amide.
14) Vitamin A acid di(*n*-decyl) amide.
15) Vitamin A acid diphenyl amide.
16) Vitamin A acid methyl propyl amide.

17) A pharmaceutical preparation comprising a vitamin A acid amide as set forth in any one of claims 1 to 16 inclusive in association with a compatible carrier material.

18) A process for the manufacture of the vitamin A acid esters of formula I in claim 1, which process comprises reacting vitamin A acid or a functional derivative thereof with an amine of the general formula



(II)

wherein R and R^1 have the significance given in claim 1.

19) A process according to claim 18, wherein the reaction is carried out under an inert gas atmosphere.

20) A process according to claim 18 or claim 19, wherein an acid halide is used as the functional derivative of vitamin A acid.

21) A process according to claim 20, wherein said acid halide is the acid chloride.

22) A process according to any one of claims 18 to 21 inclusive, wherein an amine of formula II in which R is absent is used.

23) A process according to claim 22, wherein ethyl amine is used as the amine of formula II.

24) A process according to claim 22, wherein methyl amine, *iso*propyl amine, butylamine, *n*-decyl amine, ethanol amine, 2-methoxy-ethyl amine, 2-diethylamino-ethyl amine, benzylamine or aniline is used as the amine of formula II.

25) A process according to any one of claims 18 to 21 inclusive, wherein an amine of formula II in which R is present and is identical with R^1 is used.

26) A process according to claim 25, wherein diethyl amine, di(*n*-butyl) amine, di(*n*-decyl) amine or dibenzyl amine is used as the amine of formula II.

27) A process according to any one of claims 18 to 21 inclusive, wherein an amine of formula II in which R is present and is different from R^1 is used.

28) A process for the manufacture of the vitamin A acid amides of formula I in claim 1, substantially as hereinbefore described with reference to Examples 1 to 4.

29) Vitamin A acid amides of formula I in claim 1, when manufactured by the process claimed in any one of claims 18 to 28 inclusive.

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